Welcome!

Mass spectrometry meets cheminformatics

Tobias Kind and Julie Leary
UC Davis

Course 2: Mass spectral and molecular data handling

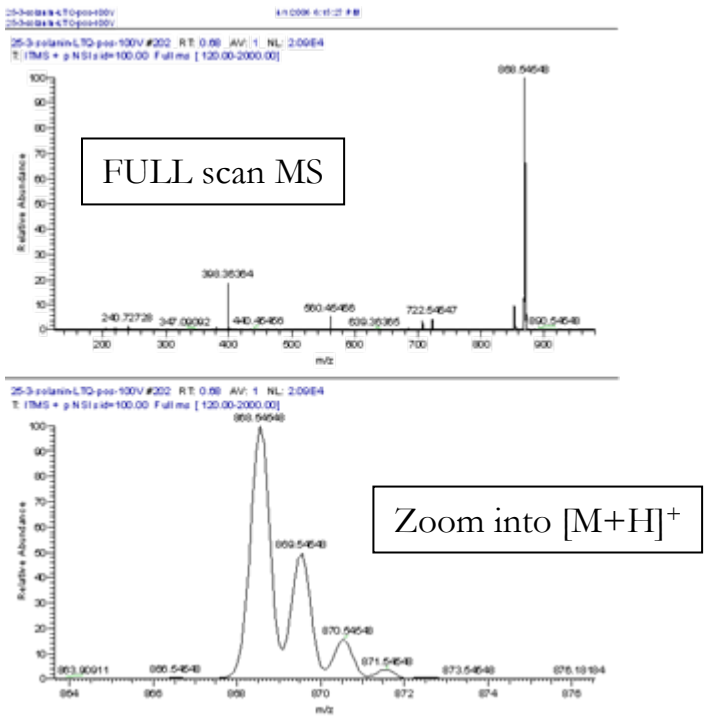
Class website: CHE 241 - Spring 2008 - CRN 16583
Slides: http://fiehnlab.ucdavis.edu/staff/kind/Teaching/

PPT is hyperlinked – please change to Slide Show Mode

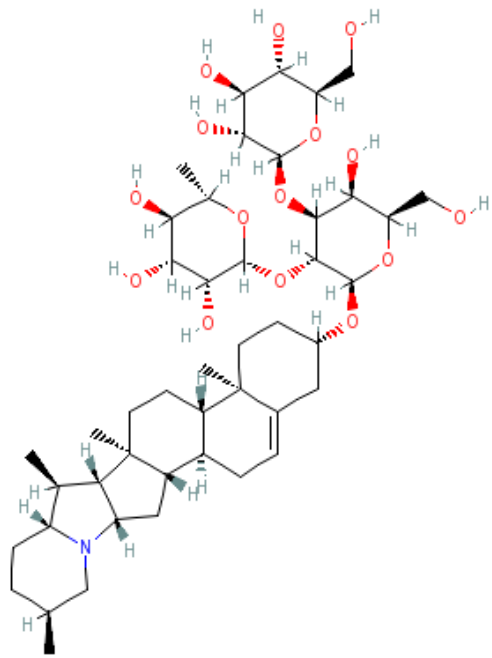
Molecules and mass spectra

Dense relationship between molecular structure and mass spectra

→ Important to handle molecular structures
→ Important to handle mass spectra and chromatograms (GC-MS, LC-MS)



ESI (pos) mass spectrum
with zoom into isotopic pattern



Solanine
(InChIKey=ZGVSETXHNHBTRK-OTYSSXIJBP)

How are mass spectra stored?

Tower of Babel – Source: Brueghel/WIKI

More than 50 vendor specific formats are known.
For every MS, LC-MS, GC-MS a single file format.
Mostly very complex data streams (formats).

For simple electron impact (EI) spectra
m/z and intensity list sufficient

Example MSP Files

```
Name: Cocaine
Formula: C17H21NO4
MW: 303
CAS#: 50-36-2;  EPA#: 113834
DB#: 32675
Num Peaks: 87
14 8; 15 15; 27 18; 28 15; 29 15;
30 11; 32 19; 39 32; 40 12; 41 68;
42 234; 43 16; 44 41; 45 10; 50 30;
51 121; 52 12; 53 41; 54 27; 55 78;
56 36; 57 43; 58 12; 59 50; 65 29;
66 15; 67 58; 68 63; 69 17; 70 30;
71 9; 74 6; 75 8; 77 355; 78 39;
79 40; 80 36; 81 125; 82 999; 83 367;
84 36; 91 47; 92 11; 93 51; 94 366;
95 50; 96 249; 97 111; 98 10; 100 11;
105 296; 106 30; 107 18; 108 54; 109 12;
110 18; 114 4; 118 9; 119 36; 120 22;
121 10; 122 88; 123 15; 124 11; 135 6;
138 7; 140 10; 150 27; 151 4; 152 38;
153 7; 154 14; 155 23; 166 32; 179 4;
180 19; 181 59; 182 716; 183 83; 184 8;
198 95; 199 12; 272 69; 273 14; 303 172;
304 37; 305 5;
```

Metadata like
CAS, MW, Formula

m/z - intensity pairs

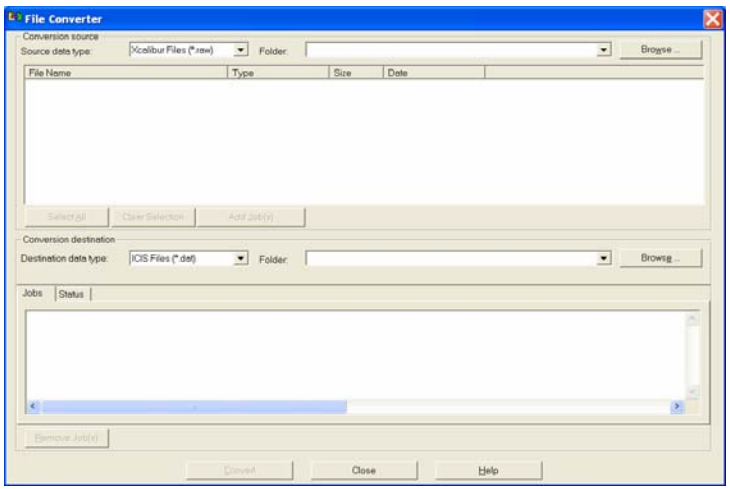
For complex MS/MS data, accurate masses,
ionization voltage and instrument method needed

Example Thermo Finnigan RAW file:

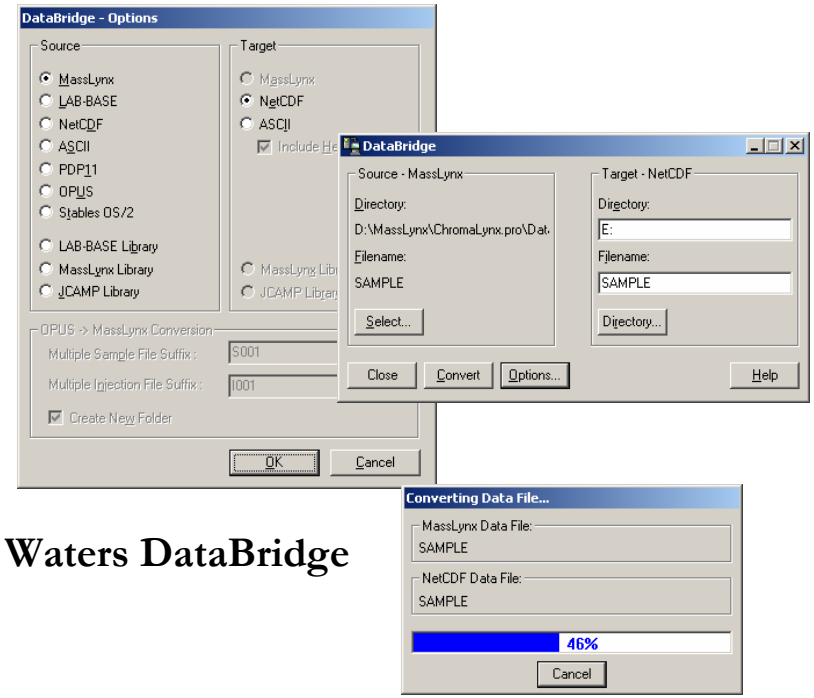
```
data_dependent_02 #1 RT: 0.0082

Total Ion Current:          2268344.00
Scan Low Mass:               150.00
Scan High Mass:              1000.00
Scan Start Time (min):       1.01
Scan Number:                 33
Base Peak Intensity:         100761.00
Base Peak Mass:              180.95
Scan Mode:              + c Full ms [150.00-1000.00]

Instrument Data:
================
Micro Scan Count:       3
Ion Injection Time (ms):                    199.98
Scan Segment:           1
Scan Event:             1
Elapsed Scan Time (sec):                    1.89
API Source CID Energy:                      0.00
Resolution:             Low
Average Scan by Inst:   No
BackGd Subtracted by Inst:                  No
Charge State:           0
```

Inter-conversions of mass spectra

Issue: Its an extreme hassle, data may get lost, may require license
Solution: Open exchange formats (JCAMP, netCDF, mzXML)
Problem: how to convert complex mass spectral MS experiments?



Thermo FileConvert



Waters DataBridge

See helper applications MassTransit
See helper applications ms-utils.org
See helper applications Lib2NIST

Mass Spectra – Importance of Metadata

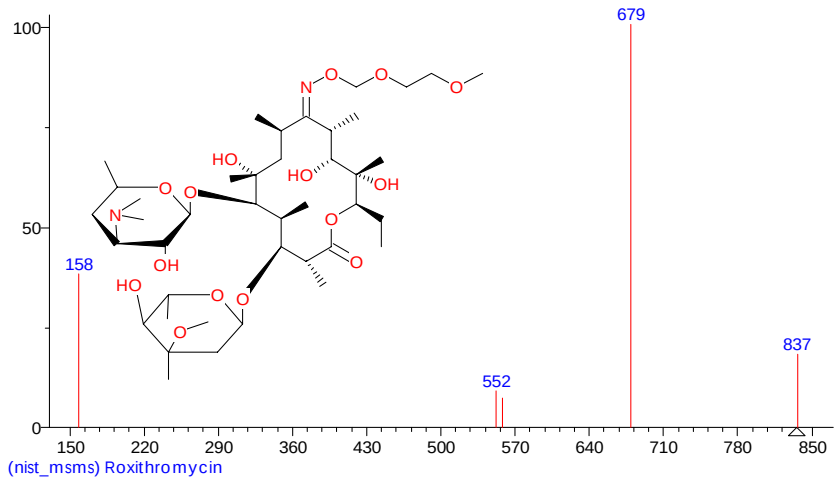
Name: Roxithromycin
Formula: C41H76N2O15
MW: 836 CAS#: 80214-83-1 NIST#: 1005429 ID#: 2064 DB: nist_msms
Other DBs: None
Comment: Draisci R. J CHROMATOGR A 926 (1) 97-104 2001
Instrument type QqQ/triple quadrupole
Spectrum type ms2
Compound type M
Precursor type [M+H]+
Precursor m/z 837.53
Collision energy 25 eV
Instrument PE Sciex API III Plus
Ionization ESI
Ion mode P
Collision gas Ar
Pressure gas target thickness 3.00x10+15 atoms/cm2
5 largest peaks:

679 999 |	158 380 |	837 180 |	552
90 |	558	70 |	

5 m/z Values and Intensities:

158 380 |	552	90 |	558
70 |	679 999 |	837 180 |	

Synonyms:
no synonyms.



Different MS techniques deliver different mass spectra
Information must be captured (best via XML)

Open Exchange formats for mass spectra

Why? You're in a successful lab using multiple vendor mass spectrometers.
Why? You want to share and receive mass spectra from colleagues.
Why? Future grants will require depositing of mass spectra in repositories.

Common exchange formats

- JCAMP-DX format for mass spectrometry
- netCDF format for hyphenated data (LC-MS, GC-MS)
- mzXML format for (LC-MS and MS/MS)

Formats for proteomics

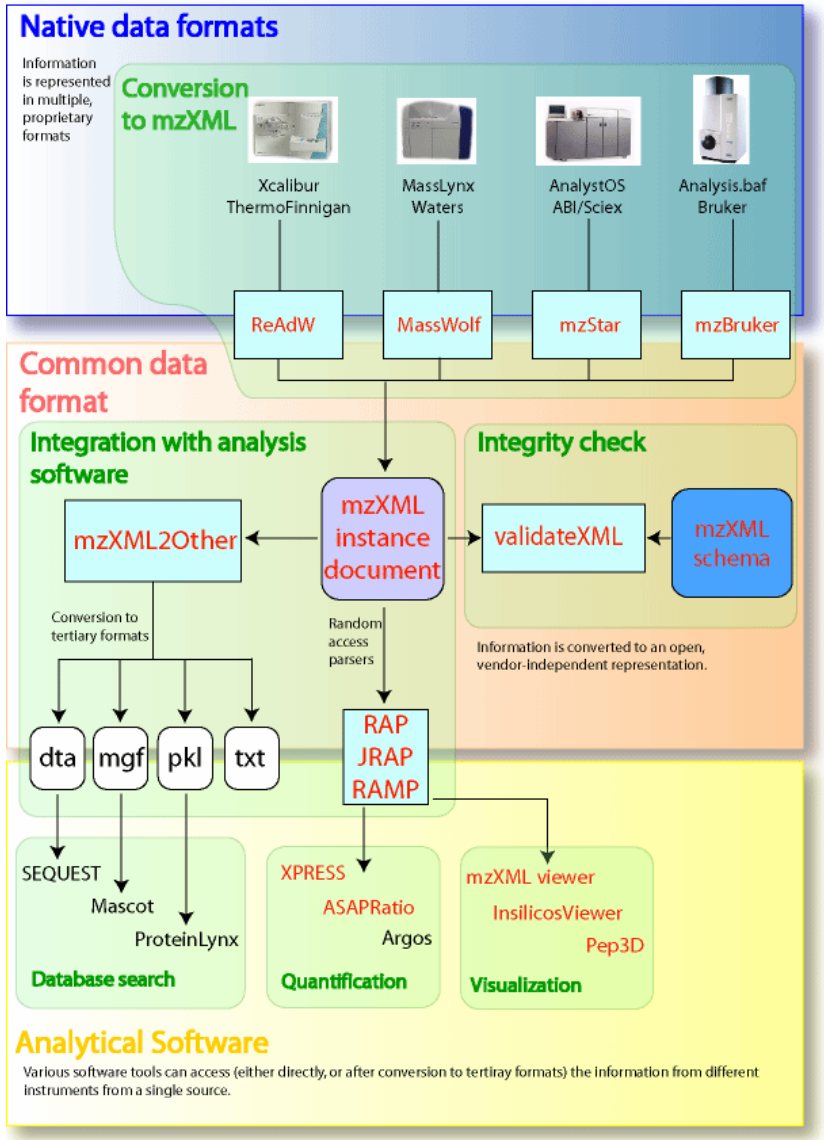
- mzData (PSI proteomics standard Initiative)
- mzXML (Seattle Proteome Center, sashimi)

} New: mzML

→Ask vendors for multiple export options, proprietary formats are no good
→Format converters are only temporary solutions

mzXML format for LC-MS/MS data

Dta, mgf, pkl files hold MS/MS spectra for database search



Picture Source:
Seattle Proteome Center (SPC)
NHLBI Proteomics Center at the Institute for Systems Biology
http://www.proteomecenter.org

How does mzXML look like?

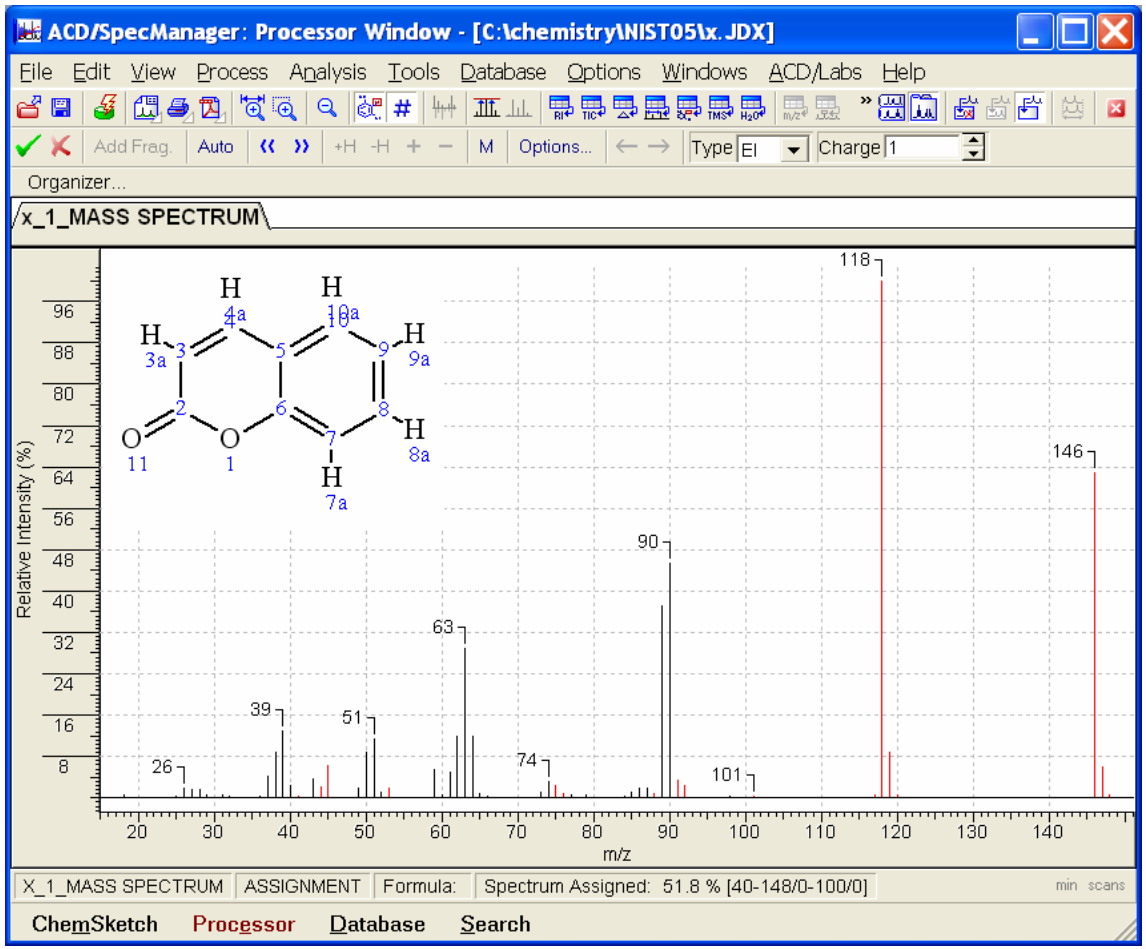
```
<?xml version="1.0" encoding="ISO-8859-1"?>
<msRun
 xmlns="http://sashimi.sourceforge.net/schema/"
 xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
 xsi:schemaLocation="http://sashimi.sourceforge.net/schema/
http://sashimi.sourceforge.net/schema/MsXML.xsd"
 scanCount="4140"
 startTime="PT120.030000S"
 endTime="PT5880.790000S">
  <parentFile fileName="raft0020.mzXML"
              fileType="RAWData"
              fileSha1="da39a3ee5e6b4b0d3255bfef95601890afd80709"/>
  <instrument manufacturer="ThermoFinnigan"
              model="LCQ Classic"
              ionisation="ESI"
              msType="Ion Trap">
    <software type="acquisition"
              name="ICIS"
              version="8.4"/>
  </instrument>
  <dataProcessing>
    <software type="conversion"
              name="dat2xml"
              version="0.1"/>
  </dataProcessing>
  <scan num="1"
        msLevel="1"
        peaksCount="959"
        retentionTime="PT120.030000S"
                      startMz="400.0000"
                      endMz="1400.0000"
        lowMz="400.3742"
        highMz="1399.3711"
                      basePeakMz="534.2230"
                      basePeakIntensity="913904.0000"
                      totIonCurrent="31883915.0000">
    <peaks
precision="32">Q8gv5kaBhgBDyLU0RpCAAEPJNhBGPfgAQ8m6CEcGnQBDyhmYP4AAAEPK
p9RGM/QAQ8sQIEXgEABDy2RGRgC8AEPL67pGs04AQ8xrDkW/EABDzLrgRw8kAEPNDf5GA
cgAQ82t2kaDSgBDzjg8RWwyABErVXqRn/oAESteQhHMewARK2RED+AAABErbF0R0AdAEStz
QhHBX4ARK3lZEca2QBErgrWRmooAESuIAA/gAAARK5apEcuAABErnnURijkAESuk+BGzO4A
RK7Bykc2RgBEruvgRo+0AA==</peaks>
  </scan>
  <scan num="2"
```

compressed data

General Structure of XML data

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<msRun ..>
        <instrument>
                …
        </instrument>

        <dataProcessing>
                …
        </dataProcessing>

        <scan num="1“>
                …
        </scan>

        <scan num=“2“>
                …
        </scan>

        <index name=“scan”>
                <offset id="1">849</offset>
                <offset id="2">11405</offset>
                <offset id="3">12072</offset>
                <offset id="4">20708</offset>
                …
        </index>
</msRun>
```

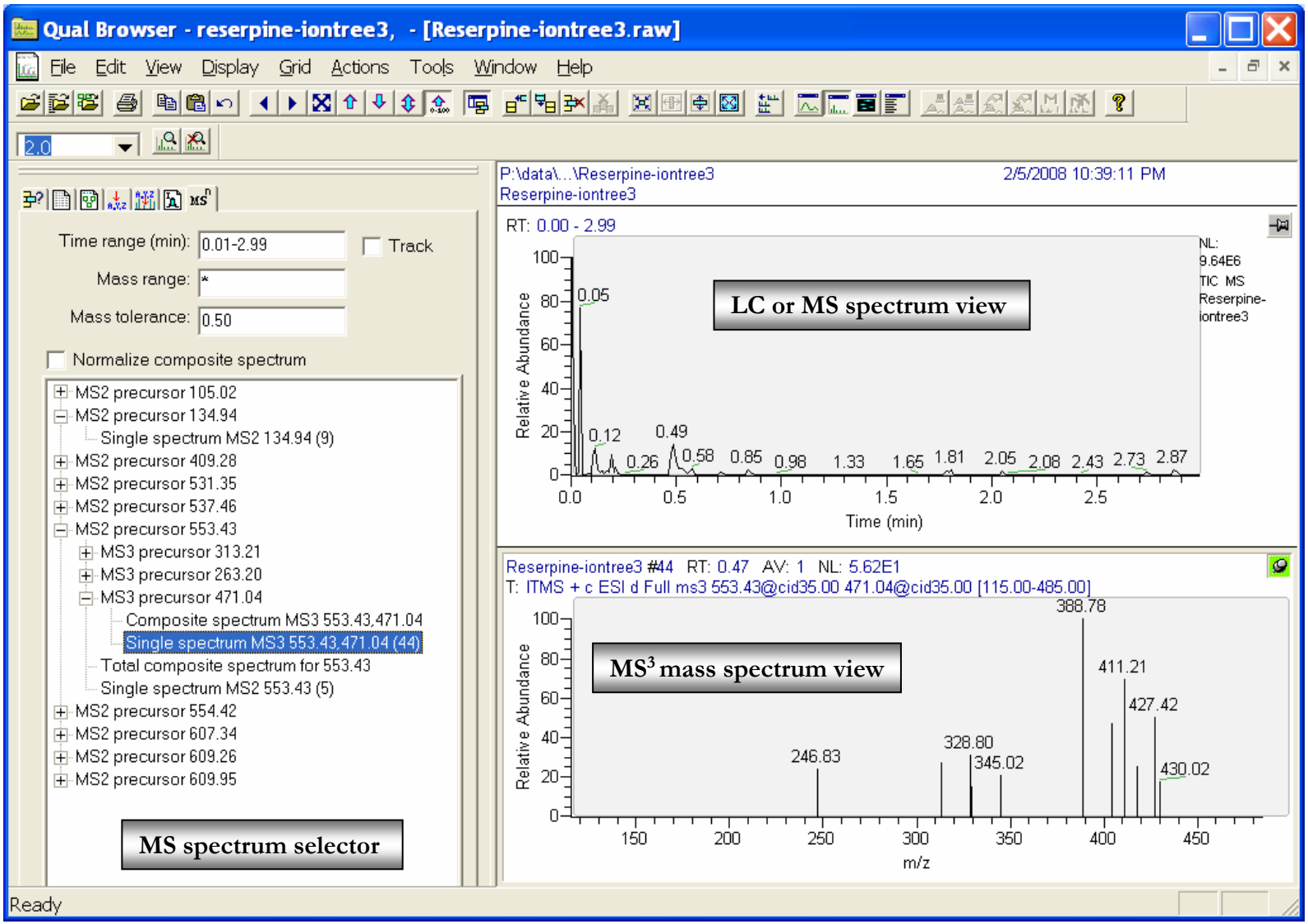
Mass spectral data handling ACD/SpecManager



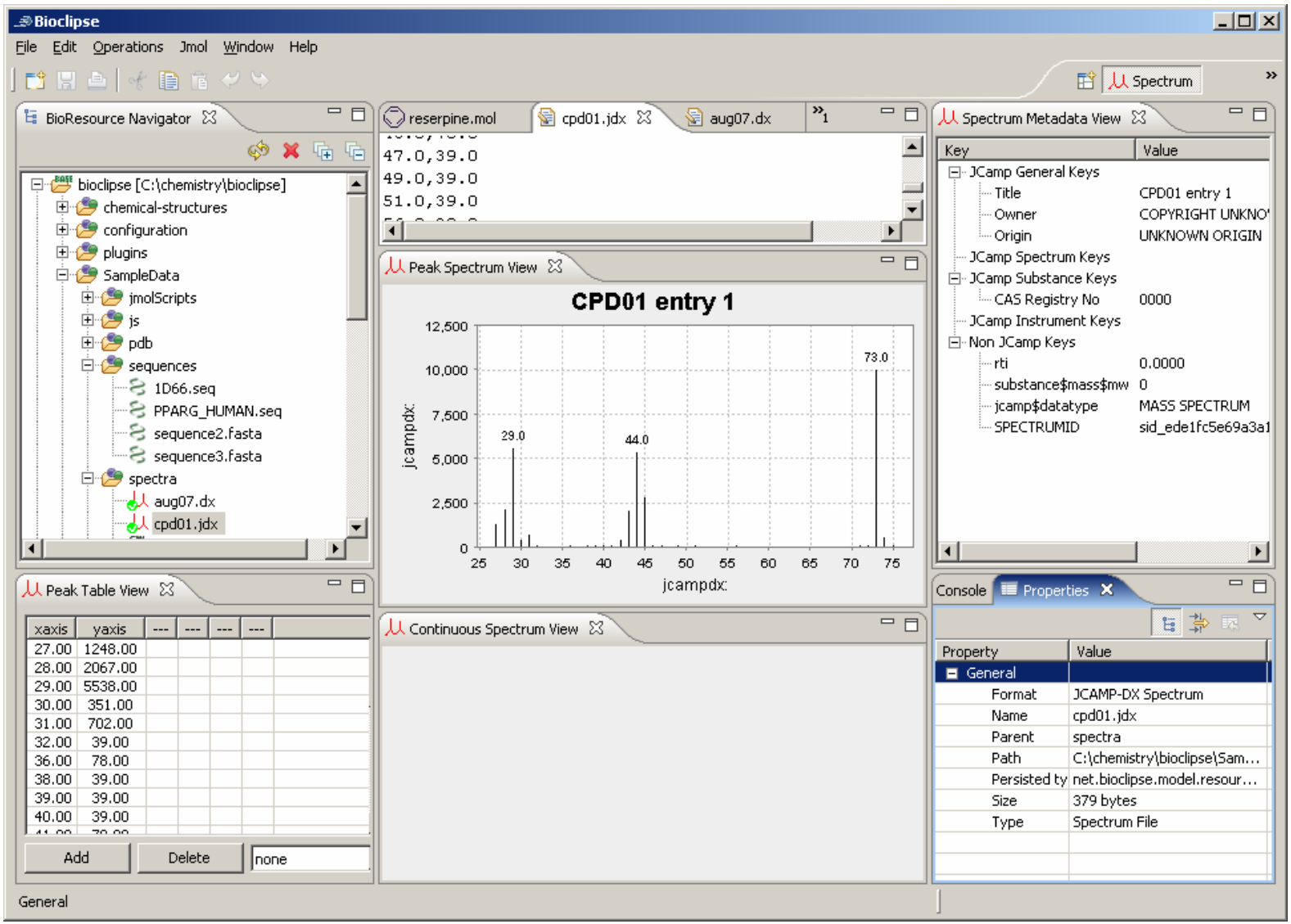
- Can handle multiple formats
- Can do spectral annotations
- Can store spectra in database

See also HighChem MassFrontier
See also NIST MS Search

MS data handling - Thermo XCalibur example



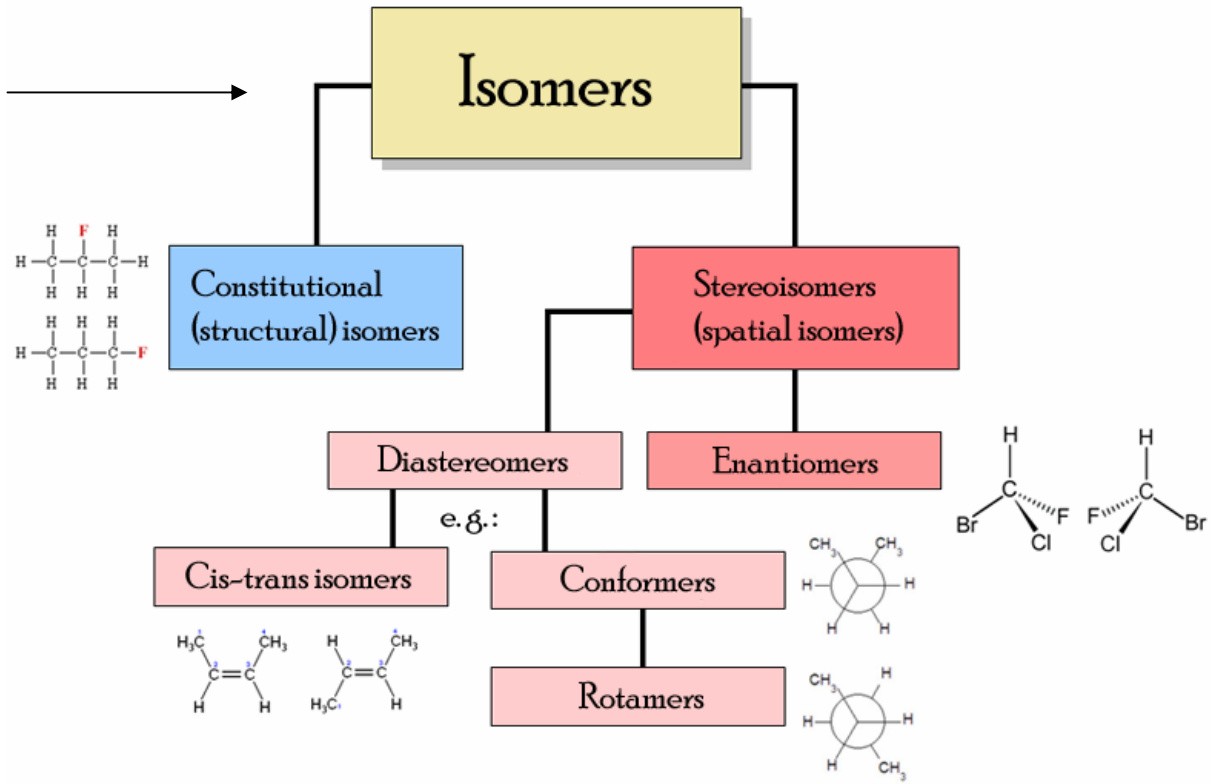
BioClipse showing JCAMP file

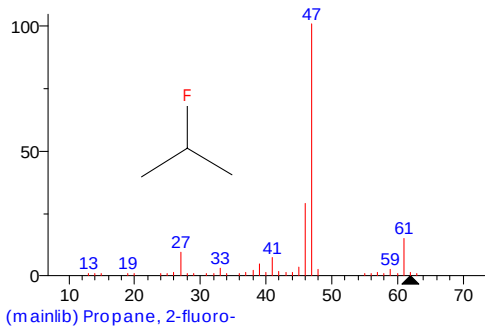


Organic Chemistry Reminder

Molecular Formula

C_3H_7F

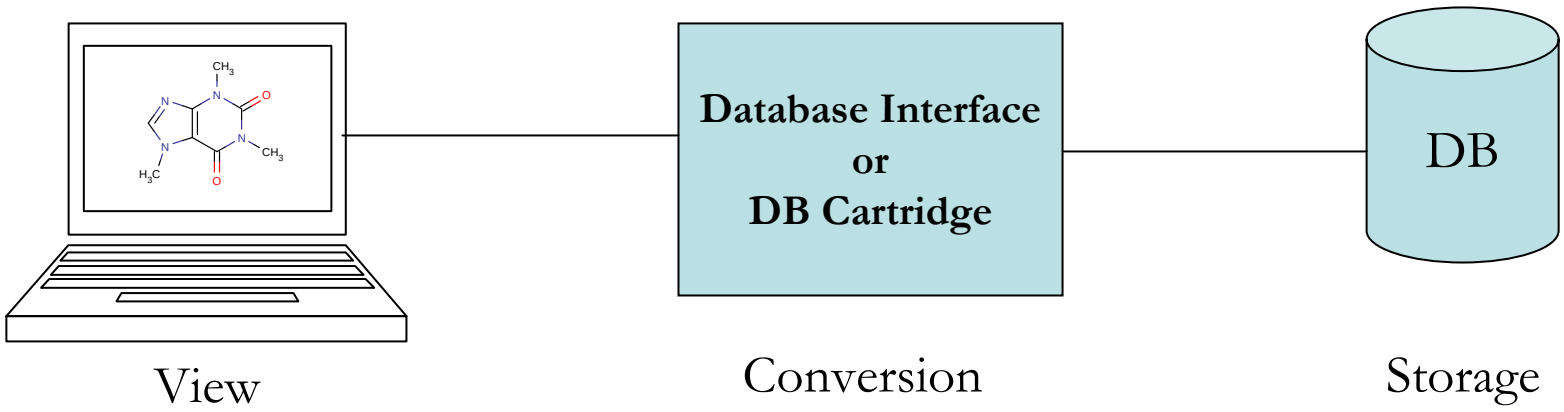




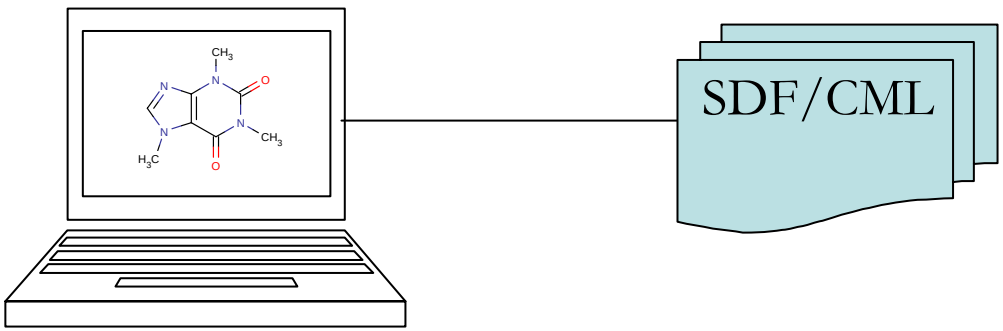
Picture source: WIKIPEDIA
MS source: NIST05

Where are structures stored? (same for spectra)

A) In databases – for millions of structures



B) In structure files (text files) – for few structures



How are structures stored?

…here cometh the (true) tower of Babel again
…more than 100 different file formats in use

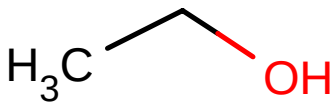
Tower of Babel – Source: Brueghel/WIKI

Structure formats can store 1D, 2D and 3D coordinate information and metadata

CCO

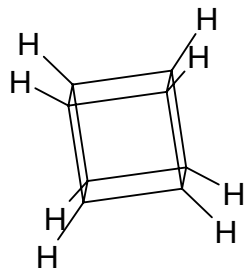
1D

InChI=1/C2H6O/c1-2-3/h3H,2H2,1H3
InChIKey=LFQSCWFLJHTTHZ-UHFFFAOYAB



2D

InChI=1/C2H6O/c1-2-3/h3H,2H2,1H3
InChIKey=LFQSCWFLJHTTHZ-UHFFFAOYAB

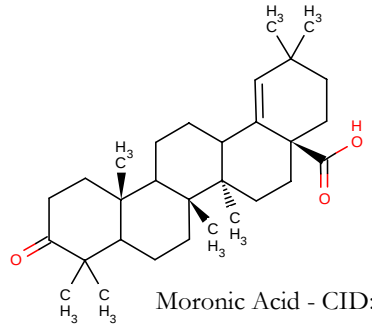


3D

InChI=1/C8H8/c1-2-5-3(1)7-4(1)6(2)8(5)7/h1-8H
InChiKey=TXWRERCHRDBNLG-UHFFFAOYAL

InChiKey Source: ChemSpider

Chemical Structure Handling



Moronic Acid - CID: 489941

Most common structure formats you need to know:

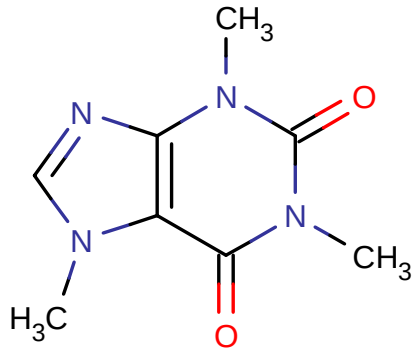
SMILES/SMARTS - **S**implified **M**olecular **I**nput **L**ine **E**ntry **S**pecification
SDF/MOL - **S**tructure **D**ata **F**ile
InChI/InChIkey - IUPAC **In**ternational **Ch**emical **I**dentifier
PDB - **P**rotein **D**ata **B**ank
CML - **C**hemical **M**arkup **L**anguage

Some problems:

- Data format needs to be based on Open Standard (problem with SMILES, ok with CML)
- Stereo and aromatic bond information needs to be saved (ok with SDF)
- Format needs to be small in space for millions of compounds (ok with SMILES)
- SMILES notation needs to be unique (problem with SMILES)
- Structure representation should be portable and based on Open Standard (ok with CML)

Chemical Structure Identifiers

Structure Identifiers are needed for uniquely identifying structures
Important for searching chemical structures in text and databases



Structure Name – IUPAC name or common name	**1,3,7-trimethylpurine-2,6-dione**
CAS RN – Chemical Abstracts identifier	**58-08-2**
PubChem ID – PubChem Compound ID	**CID: 2519**
InChIKey – Short representation of InChI	**InChiKey=RYYVLZVUVIJVGH-UHFFFAOYAW**
InChI – IUPAC **In**ternational **Ch**emical **I**dentifier	**InChI=1/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3**

SMILES structure format

Positive: Good for storing structures in single line
Fast text based search possible; human readable
Negative: Many different SMILES codes exist
SMILES for same structure can be different (canonical or unique SMILES needed)

C

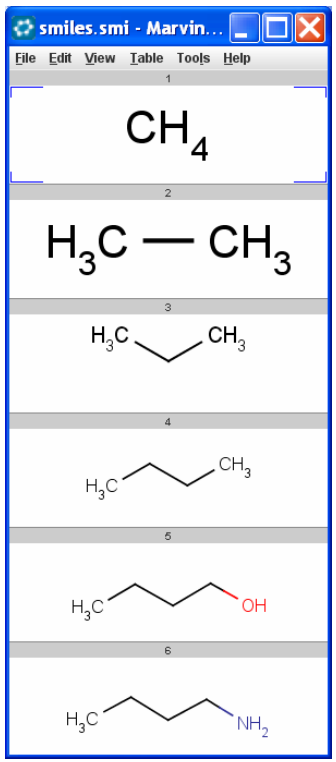
CC

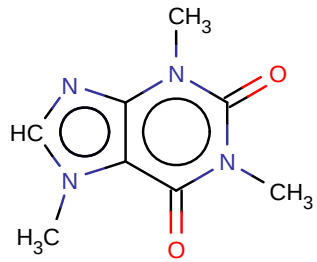
CCC

CCCC

CCCCO

CCCCN





InChI=1/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3

All those SMILES codes represent caffeine

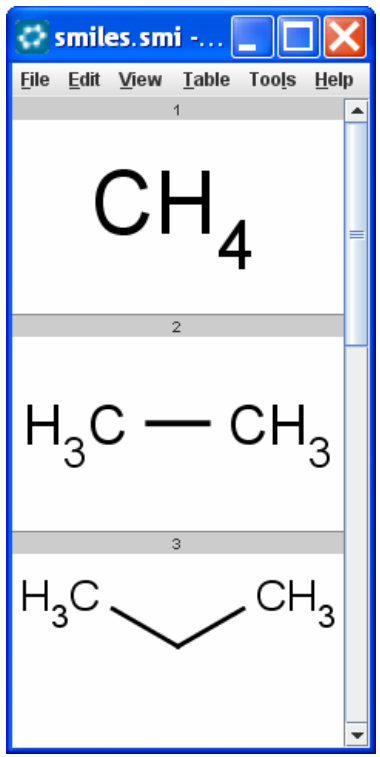
[c]1([n+]([CH3])[c]([c]2([c]([n+]1[CH3])[n][cH][n+]2[CH3]))[O-])[O-]
CN1C(=O)N(C)C(=O)C(N(C)C=N2)=C12
Cn1cnc2n(C)c(=O)n(C)c(=O)c12
Cn1cnc2c1c(=O)n(C)c(=O)n2C
N1(C)C(=O)N(C)C2=C(C1=O)N(C)C=N2
O=C1C2=C(N=CN2C)N(C(=O)N1C)C
CN1C=NC2=C1C(=O)N(C)C(=O)N2C

Caffeine SMILES Source InChI FAQ

SDF/MOL structure format

Positive: established standard format; good for storing structures safely
can store 3D structure; can store metadata (boiling points, toxicity, mass spectra)

Negative: large file size, need compression



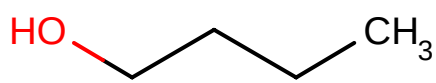

```
 OpenBabel02240823422D

  1  0  0  0  0  0  0  0  0  0  0999 V2000
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0
M  END
$$$$

 OpenBabel02240823422D

  2  1  0  0  0  0  0  0  0  0  0999 V2000
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0
  1  2  1  0  0  0
M  END
$$$$

 OpenBabel02240823422D                                  <-- Creator

  3  2  0  0  0  0  0  0  0  0  0999 V2000
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0     <-- Coordinates for 3D
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0
    0.0000    0.0000    0.0000 C   0  0  0  0  0  0
  1  2  1  0  0  0
  2  3  1  0  0  0                                      <-- Connection of atoms
M  END
$$$$
```

CML structure format

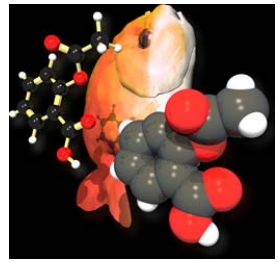
Positive: Open Standard format; good for storing structures safely machine readable

Negative: huge files; redundant information; needs compression

```
<?xml version="1.0" ?>
<molecule id="m1">
 <atomArray>
  <atom id="a1" elementType="C"
      x2="2.6673582436560714" y2="0.3080000000000006" />
  <atom id="a2" elementType="C"
      x2="1.3336791218280362" y2="-0.46199999999999997" />
  <atom id="a3" elementType="C"
      x2="4.440892098500626E-16" y2="0.30800000000000016" />
  <atom id="a4" elementType="C"
      x2="-1.3336791218280348" y2="-0.4620000000000002" />
  <atom id="a5" elementType="O"
      x2="-2.6673582436560705" y2="0.3079999999999997" />
 </atomArray>
 <bondArray>
  <bond atomRefs2="a1 a2" order="1" />
  <bond atomRefs2="a2 a3" order="1" />
  <bond atomRefs2="a3 a4" order="1" />
  <bond atomRefs2="a4 a5" order="1" />
 </bondArray>
</molecule>
```



Tools for chemical structure conversion



Example: Free OpenBabel – can handle around 100 formats

OpenBabelGUI

File View Help

---- INPUT FORMAT ----

smiles -- SMILES format

Use this format for all input files (ignore file extensions)

C:\chemistry\mopac7\mopac2007\

Input below (ignore input file)

CCO

Format Info

CONVERT

min warning level displayed

Start import at molecule # specified

End import at molecule # specified

Continue with next object after error, if possible

Attempt to translate keywords

Delete hydrogens (make implicit)

Add hydrogens (make explicit)

Add Hydrogens appropriate for pH model

Convert dative bonds e.g.[N+]([O-])=O to N(=O)=O

Center Coordinates

Combine mols in first file with others having same name

Convert only molecules matching SMARTS:

Convert only molecules NOT matching SMARTS:

---- OUTPUT FORMAT ----

sdf -- MDL MOL format

Output file

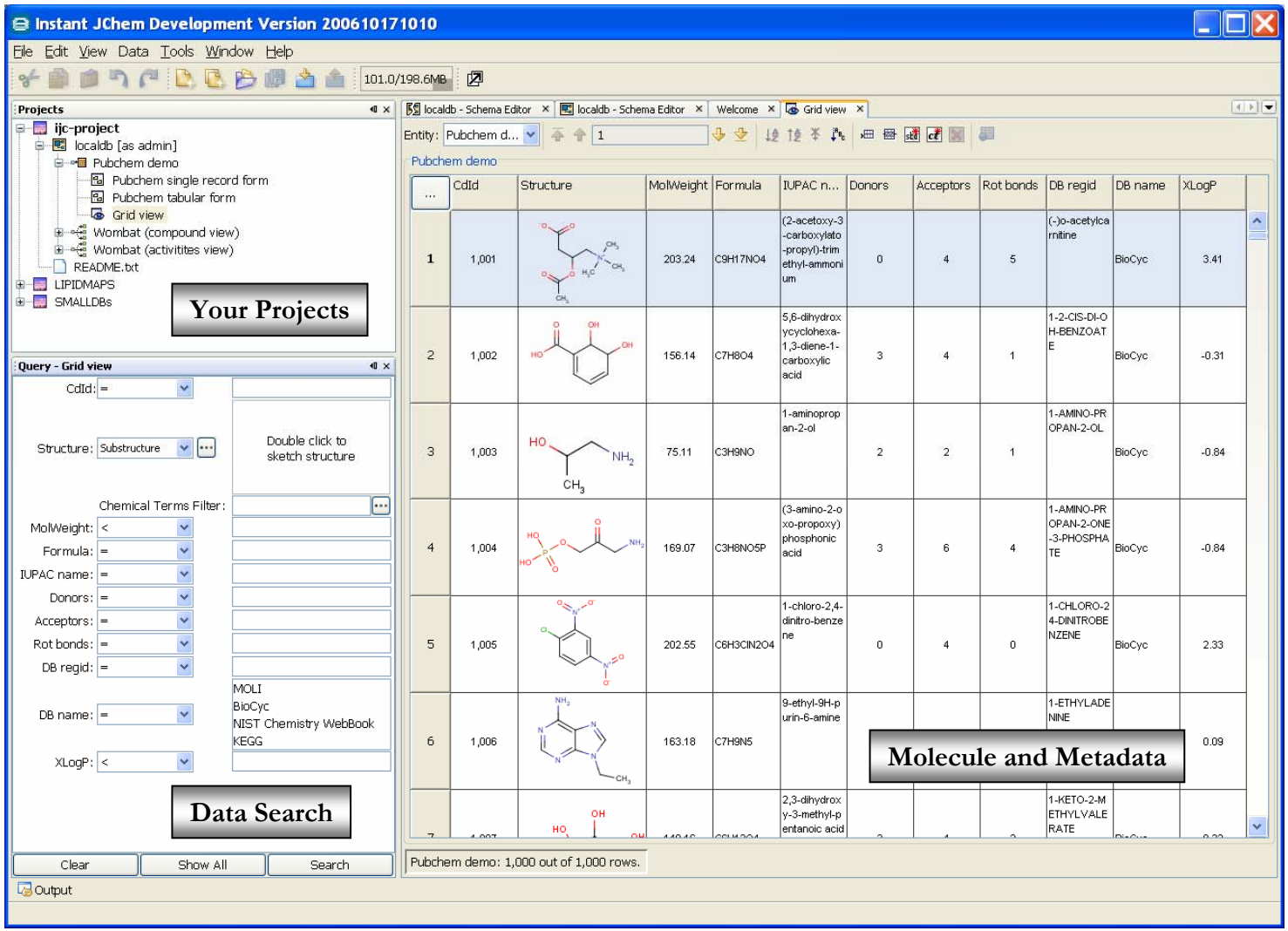
Output below only (no output file)

```
1 molecule converted

OpenBabel02240816342D

 3  2  0  0  0  0  0  0  0  0  0999 V2000
  0.0000    0.0000    0.0000 C   0  0  0  0  0
  0.0000    0.0000    0.0000 C   0  0  0  0  0
  0.0000    0.0000    0.0000 O   0  0  0  0  0
 1  2  1  0  0  0
 2  3  1  0  0  0
M  END
$$$$
```


OpenBabel is community developed (PC,LINUX,MAC)

See also ChemAxon molconvert

Handling molecules on your PC – Instant-JChem



Best way to handle structures on your PC/MAC
Up to one million molecules ok on slow PC

Download Instant-JChem

The Last Page - What is important to remember

There are different exchange formats for mass spectral data
→ netCDF, JCAMP, mzXML

Metadata must be stored together with mass spectra
Mass spectra should be published in machine readable format (not on paper)
Open Data formats for mass spectral data (in XML) are important

There are different exchange formats for chemical structures
→ SMILES, SDF, MOL, PDB, InChIkey, PDB, CML

Open Data formats and identifiers for chemical structures are important

Tasks (30 min):

1) Install BioClipse (MAC/PC/LINUX) and open some of the included JDX spectra or structures [LINK]

2) Install Instant-JChem (MAC/PC/LINUX) – create a local demo database and import the LMSD Structure-data file (SDF) [LINK]

3) For diligent students or proteomics PhD candidates:
   goto http://www.ms-utils.org/wiki/pmwiki.php/Main/SoftwareList
   http://www.proteomecommons.org/tools.jsp
   http://tools.proteomecenter.org/software.php
   http://ncrr.pnl.gov/software/
   and install one viewer or one visualizer software for MS data.

   Additionally explain what dta, mgf, pkl files are.

Literature (15 min):

Reporting standards for Metabolomics

The HUPO proteomics standards initiative -
easing communication and minimizing data loss in a changing world

Used Links

http://www.bioinformaticssolutions.com/products/peaks/proteinID.php
http://geoffhutchison.net/files/BabelTalk04.pdf
http://www.google.com/search?hl=en&q=smiles+sdf+smarts+sdf+ppt&btnG=Search
http://depth-first.com/articles/2007/09/26/pubchem-for-newbies
http://depth-first.com/articles/2007/01/24/thirty-two-free-chemistry-databases
http://scholar.google.com/scholar?hl=en&lr=&sa=G&oi=qs&q=cml+portable+open+markup+author:h-rzepa
http://wwmm.ch.cam.ac.uk/inchifaq/